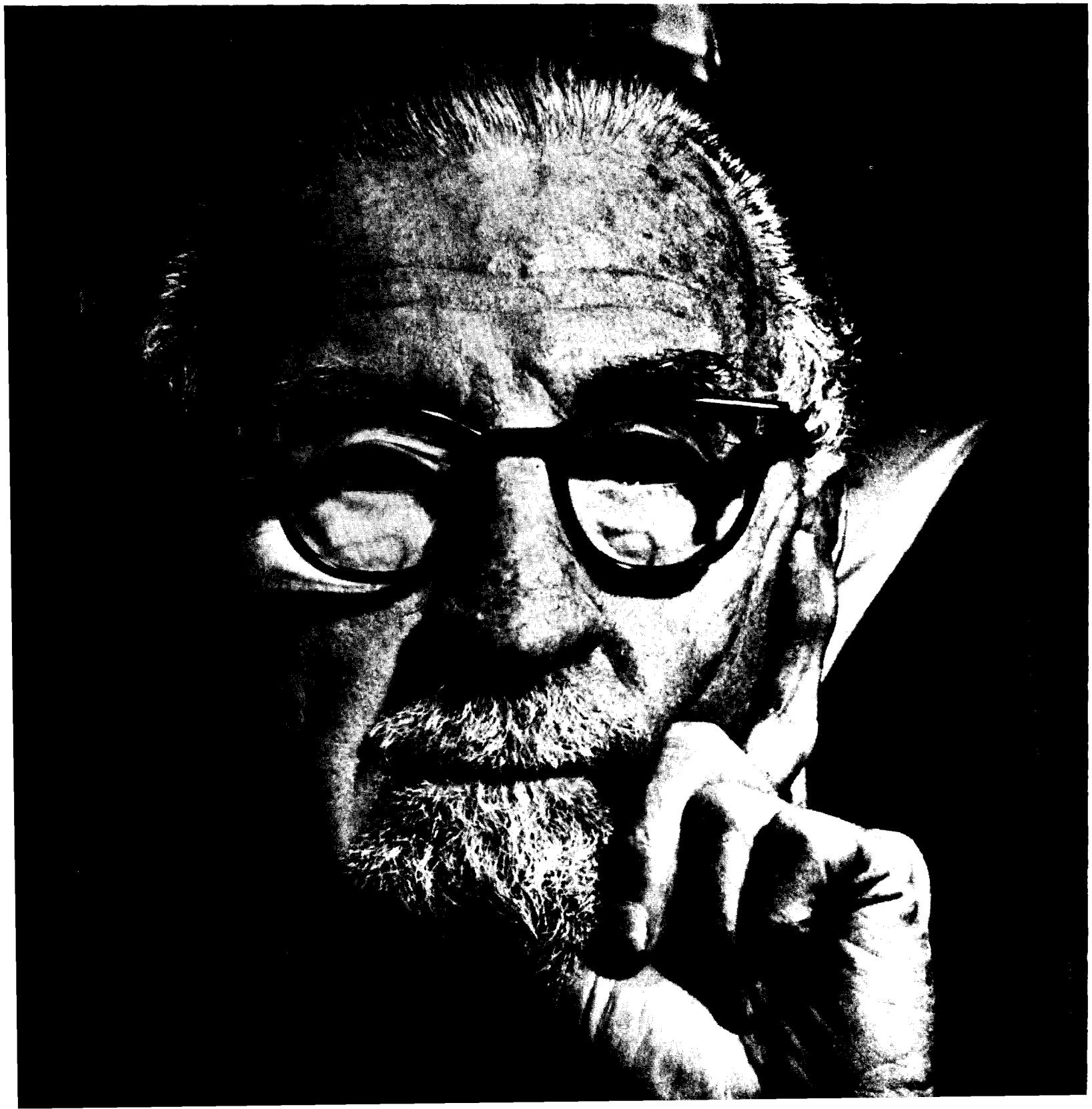
Stanford M.D.

Spring 1973 *Vol. 12, No. 2*

STANFORD MEDICAL ALUMNI ASSOCIATION



206

The Perfection of Man

Social and ethical factors will be increasingly important in determining the application of new genetic advances.

by JOSHUA LEDERBERG, Ph.D.

THIS ESSAY is intended to be a glimpse of the future as a way of celebrating the history of an exciting era in biological science. The hazards of prophecy (not least to the prophets) are well known. Still, it would be a relatively simple task to post lookouts at the frontiers of contemporary insight and knowledge in fields like genetics and molecular biology. If, mercifully, our range is confined to the next 25 years, shrewd observers may miss no more than half of the significant questions that will unpredictably emerge and may score even better in outlining the solutions to some of the major problems that are clearly recognized—like the structure and development of the nervous system, immunity, or neoplasia. We should, however, be uneasy (or delighted, according to one's temperament) about the prevalent mood that tells that most of the really exciting fundamental questions have been answered—for history teaches that this often foretells a new scientific revolution that could shake our beliefs to their very roots.

This purview is based on an autonomous model of science that has uncertain durability. Perceived ignorance (or error) is postulated to be the main orienting influence in scientific activity. Paradoxically, the more we know, the better we perceive what we do not; hence, the process is inherently autocatalytic. We should, then, be able to judge the main directions of scientific development as the exploration of the *known unknown*. The main uncertainty is the liability of all autocatalytic processes to burgeon unexpectedly in scale, or in direction, in response to imperceptible fluctuations.

A glance at the national research budget over the last five years is enough to deflate the political plausibility of this model. The overall growth of science is clearly not autocatalytic, and, increasingly, other issues of political and social choice override the opportunity presented by perceived ignorance as determinants of investment and support.

On the one hand, the central flow and apportionment of research funds is increasingly tied to specific technological missions, like cleaning up the environment or curing cancer. On the other, the autonomy of the research laboratory is increasingly caught up in irresistible pressures at the periphery for social goals that are orthogonal to scientific knowledge: equal opportunity in education and employment for minority groups and women, amenities for the local community, and the ideals of participatory democracy. (The laboratory, of course, did serve other masters in the past—viz., the ego-aggrandizement of the chief Forscher, or the central motifs of the industrial-capitalist culture.) Specific research projects are also under increasingly severe scrutiny by polarized cults of critics on issues like the exploitation of human subjects, relevance (intended by the investigator or not) to the military capability of the country, or potential abuse in conflicts over welfare assistance and population policy.

These pressures are bound to impinge on the conduct of science through their influence on institutional support but, of equal importance, on the recruitment of students and perhaps, above all, on the morale of the investigators themselves.

It follows, then, that the future course of biological research will be influenced only in limited measure by its technical opportunities, even as far as they can be observed from the existing frontier. The prophet must also foresee the outcome of complexly interwoven trends in the ethics, politics, economics, and social structure of the entire culture in which science is embedded. No contingency more dreadful than large-scale nuclear warfare can be imagined. If even this can hardly be dismissed with the confidence of a logically-rigorous demonstration, how much more precarious are our predictions that bypass many other tempests.

I am scarcely qualified to enlarge the reader's previsions of the larger scene. What is manifest is that scientists will be less and less indulged as innocents, that they will be increasingly bewildered if they do not attend to the social forces that rive our milieu. Indeed, we may have to take a more positive role in leading the culture through the religious crisis that scientific skepticism has done much to edify. To understand how "society" will deal with science demands a deeper understanding of how science is perceived by the public, and how scientific progress influences the welfare of everyman. The noisiest grievances about science (or

From *Challenging Biological Problems, Directions Toward Their Solution*. Edited by John A. Behnke. Oxford University Press, New York, 1972.

technology) have to do with weaponry and with environmental ravagement. An even more durable complaint may be the Luddites'—that new machines deprive men of a sense of worth in their work by unregulated technical progress that outpaces human adaptability.

Scientists should also seek a deeper understanding of their own profession—what inspiration and discovery really consist of and the forces that mold the choice of researchworthy problems. They may then be more likely to face up to the rationalization of their work (even in ways that may lead to their own technological displacement); for example, through more efficient dissemination of research literature or through the development of computers to undertake lower level "cerebral" functions (Feigenbaum et al., 1971). Can we believe that we have an ideal understanding of the innate talents and learned skills required for most effective performance in different fields or that the disciplines themselves are most effectively and adaptively organized?

This preamble may be summarized with a presumptuous assertion that limits to the development of scientific knowledge of life are no longer technical ones. The elucidation of the "secret" of heredity, the replication of DNA, leaves no doubt that the basic principles of many other mysteries of biology are also tractable by similar methods. We have no need to invoke an *élan vital,* other than sheer complexity of organization, to account for the special attributes of life. (That complexity remains, however, an effective and formidable guardian of the freedom of the individual will in any practical test.) It follows that further advances in biology will be dictated by the problems that biologists choose to attack; this, in turn, will be enforced by social policy to a far greater degree than in the past. An inevitable corollary is exposure to the crossfires of political conflict over the definition of the social good. There are many signs to justify Aron's (1968) prediction that the fundamental conflict may be between relative-egalitarian versus absolute-efficient conceptions of ethical utilities. (Which is preferable: to live in a levelled society free of disparity or a stratified one, whose pyramid may rise from a higher base?) Biologists, as imputed experts on the diversity of organisms, will face many dilemmas over this social conflict of equality and efficiency (Lederberg, 1972).

The long-run possibilities of biological technology are unbounded—even mortality may become a matter of definition of the rate of change of memory and personality (converging, then, with the consoling reassurances of the great religions), as we contemplate the gradual but increasingly foreplanned replacement of outworn molecules. But, in the short run, everyone still dies, and too many die prematurely according to any ethical standard. Futuristic pretensions about genetic engineering are a mockery to a mother who has delivered a trisomic child. And we are still unable to tell the offspring of a Huntington's choreic whether he will transmit the disease to his children or, indeed, whether he will in some few years succumb himself. This disparity between present-day reality and eventual potentiality may arouse deep-seated resentments against that rosier future and even against contemporary scientists who are not quite able to bring it off—in time. Perhaps this is an argument against advertising the future, but too much indispensable planning hangs on clarifying the picture the best we can. The remainder of this essay will, however, focus on the challenges and horizons of the near future.

According to popular legend, "anything possible will be done" if the technologists get their hands on it. Anyone who is trying to do anything substantial knows that the opposite is usually true. Absent the incentives of military applications, the more sophisticated the science the greater is the distance between its conceptual opportunities and reduction to practice. One of the most egregious gaps between scientific potential and human needs is in agriculture. Formidable technical competence and human importance attach to the new introductions of dwarf wheat and rice which have promoted the green revolution. Nevertheless, the scientific foundations of these breeding ventures go little beyond the rediscovery of Mendelism in 1900. Shrewd agronomic insight, and meticulous attention to detail in the selection of parent stocks and intermediate hybrid lines, rather than innovational genetic theory, were the roots of these successes. It is likely that many more opportunities await the intelligent application of the most straightforward techniques of plant breeding. They will, in fact, be indispensable, merely to retain our present position in the face of the evolution of parasites adapted to new and homogeneous genotypes.

In principle, the cell- and molecular-genetics developed in the last 25 years could make even more incisive contributions, but it has yet to make any significant impact. Some of the fault must be laid at the door of the agricultural research establishment. But the United States Department of Agriculture must, in turn, be responsive to a community that now puts increased crop efficiency very low on its list of priorities, since bumper crops prove to be economic disasters. We are, then, relatively backward in fundamental biochemical and genetic investigations of the development of seed proteins compared to their importance in human nutrition. Until recently, the National Institutes of Health have been hard put to justify research grants on the amino acid sequence of zeins in different varieties of corn. But if we had information of this kind, to the depth of, say, our knowledge of human hemoglobins, we should be much further along in designing more efficacious sources of plant protein.

This remark does too little credit to the empirical development (International Atomic Energy Agency Panel, 1969) of hi-lysine corn. The nutritional advantage of these mutants, which have visibly altered seeds, evidently depends on the diminution of zein content and substitution by other proteins. However, the developmental mechanisms involved are still poorly understood, and we are still very far from a rational design of a seed protein optimized for human nutrition. With a more detailed analysis of gene-controlled protein sequences, we would have a firm basis for the stepwise accumulation of point mutations or recombinants toward that optimum. The substitution of threonine for serine, or of lysine for arginine, in a seed protein would be expected to have little impact on its function for the plant compared to its utility for man. Plant breeding is, of course, burdened with logistic problems of assessing intact seedlings as the units of genic expression and with the traditional problems of diploid inheritance (need for back-crosses and multiple progeny tests). These might be averted by more attention to artificial haploids and to the manipulation of plant cells in culture, including cell fusion. Similar techniques have greatly advanced our knowledge of the genetics of a species, man, which few would have expected to outstrip maize two decades ago.

Viruses (as an exemplification of plasmagenes) may also play a role. (Indeed, they already do; for example, in the control of male fertility for the production of hybrid corn.) An example of genetic engineering of a virus that may eventually be important for improving the quality of plant protein is suggested by the claim of Rogers and Pfuderer (1968) of the engineering of a tobacco mosaic virus variant to which poly-A was appended, with the concomitant production of excess polylysine. Well-defined clones of such variant viruses have not, however, been reported.

A control long-run objective for molecular agrobiology is the maximization of protein yield at the expense of polysaccharides. The plant will have to be engineered into a kind of lactating organ in which just enough structural cellulose is invested to sustain the primary utility of protein synthesis. The dwarf varieties, indeed, exhibit this very principle.

Human consumption of photosynthetic product amounts to about 300 M (3×10^8) tons of fixed carbon per year. This is only about 5 percent of the total crop yield, most of this being waste tillage. Crops, in turn, make up only 10 percent of land-cover photosynthesis; it will be at least as difficult to expand this ratio as to improve the efficiency of already cultivated lands. A rising population will have few alternatives more palatable than the use of chemically recycled cellulose or fossil carbon for human, as well as industrial, fuel.

The salvage of the world food resources is by all odds a mixed blessing, according to well-known Malthusian reasoning. It is difficult to see how striving countries will be induced to limit their population growth so long as the weight of numbers is a political, and even a military, weapon in interstate competition. The technical means of contraception are improvable, but scarcely lacking now. We have little basis for optimism except the hope that world order and economic modernization may advance in spite of the population drag, and that these factors will encourage a demographic reversal. The natural and man-made disasters that have afflicted Bengal are visions of the alternate paths.

Another crushing affliction of most of the world is infestation with animal parasites, especially malaria, blood flukes, and worms. Environmental sanitation, directed at vector control, has been the most effective public health measure to mitigate these debilitations, but tropical countries are likely to remain burdened with them for many years nevertheless. The well-defined life cycle of these parasites should make them biologically fascinating, as well as humanely rewarding, targets for more profound study with modern methods. The attenuated mutant already plays a central role in prophylaxis against virus infection by vaccination without the benefit of deep insight into the mechanism by which the parasitism is frustrated. With the flukes and worms, well-defined morphogenetic stages are involved in the progress of an infestation, and with the malaria plasmodia, it should be even easier to superimpose biochemical analyses of the critically altered stages of attenuated mutants which could confer analogous benefits in the form of virus vaccines for the control of corresponding diseases. The genetic engineering of Plasmodium falciparum vies with that of Oryza sativa as a further target of molecular genetics.

From the standpoint of scientific and technical accessibility and of clarity of ethical consequence, parasites and domesticated animals and plants are clearly the most attractive targets for genetic design. However, utopian aspirations for the "biological improvement" of man were appended to the development of genetics even before its emergence as a rigorous experimental discipline. The eugenic aspiration, of course, conflicted head on with theological doctrines of the origin of man in original sin and alternative recipes for salvation. It is refueled today by doctrines of the inevitability of evil in human nature that are fallacious deductions from ethological research.

The most telling argument for eugenics is the fear that the existing human species is doomed to self-destruction. But a culture that cannot evolve the political machinery to contain its weapons will hardly improve its competence for survival by adding biological engineering to its repertoire.

Like many other messianic visions, eugenics is faulted by a confusion between the needs of an abstract *mankind* and those of individual men and women. In many

arenas, utopian aims for the ordering of human affairs might be achieved at the sacrifice of individual liberties. In the economic sphere, "from each according to his abilities" is a plausible humanitarian ideal, but it can be enforced only with the apparatus of a police state and an arbitrary determination of what each has to contribute. Apart from the already fatal obstacles of political implementation, genetic planning faces frustrations analogous to the failures of planned economies, both with respect to technique and to the validation of consensual purposes. In the real world, social movements will continue to have much more incisive effects on the human gene pool than any conceivable technical advances that could be labelled as "tampering with the genes."

Geneticists, in the main, have been so critical of large-scale eugenics that they may forget that the allegation of seeking to breed Supermen will be renewed in every popular discussion. Some of my own efforts to outline the difficulties and paradoxes of genetic design have, for example, been misquoted (Ramsey, 1970) as advocacy. I will plead guilty to withholding categorical anathema on issues that are amenable to deeper exploration, both technically and morally. Social attitudes on questions like contraception and abortion have changed too dramatically in one or two generations to reinforce the posture of sempiternity of our ethical pronouncements, above all in human biology. This is no assurance of ever-increasing permissiveness—the history of the tides of moral fervor shows more displacement than dissipation, and they may return once again to now-abandoned shores.

Let it be clearly posited, nevertheless, that the remaking of man is an illusionary goal for the application of genetics in a liberal society.

The principal task of genetics is scientific understanding; the principal target for its applications to man is the alleviation of individual distress—which the physician cannot repudiate no matter what the general state of the world. In pursuing his goals, it should go without saying that the geneticist is bound by the same set of ethical restraints that apply to other innovative branches of medicine. The surgeon does not use his scalpel by whim, and even in the chase after potential knowledge, he is, above all, accountable by law and ethical tradition to the needs of his patient.

Table 1 catalogs a number of potential techniques that may relate to the prevention or therapy of genetic disease or which may influence genetic constitution. This is not a well-bounded arena, for all of medicine —indeed, all of culture—is potentially euphenic and eugenic. That is, they may (1) ameliorate the actual development and expression of genetic predisposition, and (2) thereby, indirectly influence the relative frequency of different genes in the population.

The boundaries of what should be called "genetic" disease are also uncertain, for every pathology must have both a genetic and an environmental component. Many common diseases, as well as overall longevity, have a significant heritability. About 5 percent of overall morbidity can be related to specific genetic defects with a relatively simple basis; if we also take account of the heritable component of prevalent diseases, like schizophrenia, diabetes, cardiovascular disease, and so on, at least a fourth of total morbidity (in medically advanced communities) must be attributed to genetic imperfections.

Genetic Load, Mutagenesis, and Environmental Hygiene

The genetic load is, therefore, a formidable part of the problems that must be faced by medical practitioners and their patients. Plainly, preventive measures should have a high priority, if we could, thereby, prevent the intrusion of genetic defects in the first instance. This may not always be possible—an unknown part of the genetic load is "segregational"; it derives from heterosis; i.e., an advantage of the heterozygote over either homozygote. Natural selection, then, tends to keep both of the alternative alleles in the population, notwithstanding the inevitable quota of impaired homozygotes that must recur at every generation.

Heterosis is important to framing reasonable expectations for genetic improvement since no freely breeding population can then be composed exclusively of the healthiest (heterozygous) phenotypes. The production of high-yielding corn is based on the careful nurturing of a number of rather weak, highly inbred strains as parent stocks which are then crossed to produce vigorous hybrids. The farmer who tries to use these, in turn, as seed corn courts disaster—a fact hardly in keeping with racist mythology or with the naiver forms of eugenicism.

Furthermore, the heritability of different diseases gives no assurance that a single optimum genotype can exist. Susceptibility to cancer may reflect a low excitability of the immune mechanism; allergy the converse. Total freedom, both from cancer and allergy, may be physiologically unattainable. We have only provocative data about mutual exclusions in predisposition to disease, but we can still be fairly sure that we have more choice about how, rather than whether, to die.

These aspects of disease genetics are relatively independent of the mutation rate, responding mainly to natural selection. They offer some room for genetic insight, short of total amelioration, since the existing gene pool has evolved in a historical context of medical and other cultural determinants that have changed far more rapidly than gene frequencies can have responded. Furthermore, Darwinian fitness, or reproductivity, is becoming less and less congruent with the standards of somatic quality by which we judge ourselves and our peers.

Table 1

*Potential Technologies of Eugenics and Euphenics (Not Confined to Man)**

A. *Selective mating:*

1) By phenotype of parents (assisted by biochemical and cytological assay)
   a) negative — distracting, discouraging, or sterilizing the "unfit"
   b) positive—
      i) encouraging select pairs
      ii) with artificial insemination, donor ("rational germinal choice")
      iii) with oval or ovarian transplant
      iv) both ii and iii, or fertilization *in vitro*, followed by implantation
      v) extracorporeal gestation (test tube baby)—*see also* euphenics

   (i–v are not very different in their *genetic* consequences)
2) By genotype of parents—as above, with deeper analysis of parental constitution. Except for specific aberrations, very little can be said at present about genetics of *desirable* traits.
3) By relationship of parents
   a) inbreeding—The main impact is to expose recessive, usually deleterious, genes: increase phenotypic variability of F_1; decrease the genotypic variability of later generations.
   b) outbreeding—antithesis of (a). Most cultures strongly encourage outbreeding.
4) By age of parents—to forfend accumulation of deleterious mutations and chromosome anomalies which increase with parental age
5) By phenotype or genotype of the zygote or of the fetus (antenatal diagnosis and voluntary abortion)—Earlier selections would avoid the trauma of aborting an established fetus.
6) By genotype of the gametes: e.g., separation of X from Y or normal from defect-bearing sperm
7) With sperm of other species (compare [1] [b] [iv])—Nothing is known of the consequences among primate species (possibly *in vitro*). All contemporary races of man appear to be freely infertile. Cross-pollination is, of course, a crucial technique in plant breeding.

B. *Innovations in Zygote Biology* — Vegetative (asexual) propagation. Cloning. (Almost universal among plant spp.)
1) Parthenogenesis—development of an unfertilized egg. (This might be genetically identical to the mother, or might be a product of meiosis, which would be an intense form of inbreeding.)
2) Regeneration — development of a whole individual from somatic tissues (as in some plants and lower animals like earthworms)
3) Differentiation of gametes from somatic tissues previously subject to extensive genetic manipulation
4) Somatic reduction in gamete-forming cells in culture (somatic inbreeding)—would allow predictable outcome of further matings from a given parent which is not now assured.
5) Nuclear transplantation—renucleation of a fertilized enucleated egg. Genetically equivalent to cloning from the source of the nucleus.
6) Embryo—splitting to produce twins or multiplets. Not to be confused with multiple ovulation (occasionally induced by fertility-promoting drugs). About one-third of spontaneous twins are monozygotic, i.e., arise from the splitting of one embryo. Note also the opposite phenomenon.
7) Embryo fusion (chimerism) — so that one individual comprises two or more genotypes. This grades into tissue transplantation at later stages. It should allow different genotypes a new latitude for mutual complementation, e.g., *mens sana in corpore sano*. Somewhat less than 1/1000 live births are spontaneous chimeras, but some of these arise by other mechanisms.

C. *Adjuncts from somatic cell biology*—For eugenic applications, these would be coupled with procedures like B(5). For euphenic effects, altered cells can be grafted back to a host or some manipulations done directly on his tissues.
1) Algeny—directed alterations of genes
   a) controversial claims of effects of DNA uptake in mammalian cells following a long tradition of genetic work with DNA in bacteria
   b) incorporation of viruses
      i) experimental tumor viruses
      ii) use of specially modified viruses
         1) vaccination to induce immunity to viruses
         2) virogenic therapy to replace missing genes
         3) virogenic enhancement for superior performance—if we but knew the biochemistry thereof
   c) incorporation of chromosome fragments transmitted by cell fusion
   d) specifically induced mutations — No plausible approaches are now apparent.
2) Random mutation and specific selection of cells with altered properties—has full precedent in strain selection in microbes. Many uncertainties relating to possible cancer potential of such implants.
3) Cell fusion to form somatic hybrids—These cells may then lose various chromosomes to give many new forms. Extends scope of (2). Can be readily applied to fuse cells from "distant" species, e.g., fish and human.
4) Development of symbiotic strains of lower species, with habitats that grade from the external world (e.g., crops) to internal to intracellular—Parasitic worms in man have evolved in this direction with the help of adaptations to thwart immunological rejection. In principle, they might be domesticated. So also might algae be trained to an intracellular habitat in man where they might photosynthesize essential nutrients, if not bulk calories, as they already do in primitive animals.

* From Lederberg, 1971*b*; see also Davis, 1970.

However, the "mutational" part of the genetic load must be considerable, and this is related to the rate of mutation (informational deterioration) in the genetic material. A certain level of mutation is an inevitable byproduct of molecular accidents in cell metabolism. However, if we argue from the relative incidence of environmental, compared with intrinsic, carcinogenesis, which may be parallel phenomena, we may judge that four-fifths of our ambient mutation rate is of environmental origin and could be eliminated by environmental hygiene (relating to drugs, food additives, and possibly some natural foods, water, and air pollutants, certain virus infections). About 10 percent of that quota can be attributed to the natural radiation background, which is essentially not avoidable, and an equal proportion to artificial radiation. At one point, nuclear power development appeared to be the main source of increasing environmental radiation, but the newly adopted standards of the AEC promise to keep this to a negligible proportion of the background. The major source of artificial radiation today, by far, is diagnostic X-rays which approximate half or more of the natural background. Our increasing sensitivity to genetic hygiene will raise agonizing issues of the costs and benefits of medical X-rays. These can hardly be answered by pointing to the overall benefit which is irrefutable. They do demand an examination of the dispensable margin, be this 10 or 80 percent of the total level of manrads now dispensed. Many physicians believe that "defensive medicine," that is, the anticipation of lawsuits for malpractice, is responsible for a needless volume of cautionary X-rays. The present legal framework compensates the single patient who might have been benefited by a routine X-ray that was negligently withheld. It does nothing for the 10,000 others or their progeny who must eventually pay some price for having been X-rayed with unimportant results. Our skills at matching these costs and benefits can only be sharpened if we are first educated to asking such questions in economic, rather than diabolic, terms.

The same issues confront us in the formulation of policy about chemical additives to the environment—solvents, drugs, food additives, and so forth. It is not very useful to assert that a compound is mutagenic without proceeding to a more quantitative evaluation of its impact, and our data on human response to chemicals is even more fragmentary than to radiation. Before joining the bandwagon against synthetics, the geneticist must caution that natural foods need a similar examination. The first authentic publication about chemical mutagenesis (Auerbach and Robson, 1944) concerned allyl-isothiocyanate, a constituent of horseradish and mustard. (This compound has, moreover, been found to induce skin tumors after local application in mice.) Mustard has not, however, been subjected to the rigors of evaluation according to the Delaney Amendment, perhaps for fear that this would overturn our simplistic approaches to a problem that is as complex biologically as it is vulnerable to the bias of vested interests. Environmental hygiene may be the most fruitful area of application of more sophisticated molecular genetic analysis.

Options for Genetic Therapy

Among these options, a few stand out for offering the most realistic opportunities for health benefits. They include:

Antenatal Diagnosis

An increasing number of diseases will be reliably diagnosed by cytological and biochemical studies on cell cultures derived by amniocentesis (Dorfman, 1972). We already have exciting advances in the understanding of several neurochemical disorders which rely upon the identification of specific enzyme defects. The techniques of cell-fusion and of chromosome identification with fluorescent stains will strengthen our ability to trace mutant genes, and similar methods will also help identify high-risk parents. We can visualize more direct assays for specific information content of DNA with techniques for the isolation of specific messenger RNA and, then, the homologous genes. The DNA segments can then, in principle, be tested in cell-free systems for protein synthesis or, perhaps, even subjected to direct analysis of their nucleotide sequences.

This level of sophistication in the analysis of gene effects should, in many cases, lead to deeper understanding of the disease and may provoke explicit therapies. Meanwhile, our main recourse is voluntary abortion of the impaired fetuses to allow a mother the best chance available to her of delivering a child free of malignant defect.

Our experience with the antenatal diagnosis of sex should help correct overanxious predictions about the anticipated misuse of "genetic engineering." This has allowed a reliable method of voluntary control of the sex of offspring for some years. Whether the sex of the fetus has ever been a controlling factor in a decision about abortion, without more persuasive indications, simply has not surfaced as a significant social problem to warrant any special regulatory controls. The common sense and patient-oriented values of the medical profession remain the most effective bulwark against nonsensical distortions of its tools.

Actually, voluntary control of the sex of offspring might encourage a limitation of family size (e.g., one boy, one girl) consistent with the social interest in overall moderation of population growth. Then, a balanced sex ratio could be maintained even under voluntary choice.

Transplantation

Many genetic defects involve cell populations as metabolic units that could be supplanted or restored

by transplantation. For example, complete transfusion plays an important part in the therapy of Rh-hemolytic anemia (but is associated with a danger of graft- vs host-immune disease when applied to the fetus). The scope of tissue transplantation should not be judged by its present limited application which is constrained by the hazard of graft-rejection. Specific ways of mitigating rejection are bound to appear as a fruit of immunobiological and immunogenetic research. We will then have a simple, practical way, for example, to deal with sickle-hemoglobin disease — namely, by transplantation of normal erythropoietic marrow to the newborn or, perhaps, the fetus. We will also surely find that many other diseases, genetic or not, are amenable to relief by tissue and organ transplants—e.g., hepatocytes for PKU and for galactosemia, or insulin-secreting cells for diabetes. The last example illustrates the opportunities for therapy even where the transplanted organ may not be the primary seat of action of a defect.

The growing popularity of transplantation of hair (auto- today; homo- tomorrow; hetero- yesterday [the obsolete fur coat]) attests to the same principle.

Transplanted immunocytes are also likely to play a key role in the treatment of auto-immune disease (perhaps, after systemic elimination of offending cells) and in the prevention and treatment of neoplasms.

In cell biology research, we have just begun to move into the arena of systematic work on the genetics of somatic cells. The discovery by Henry Harris (1970) of Oxford of powerful methods to induce the fusion of cells has attracted enormous interest in the consequences of mixing chromosomes of different genotypes and species and in their reassortment in various combinations. The way is, then, open to genetic analysis (and genetic engineering) of mammalian and human cells in a way that would have been technically and ethically impossible otherwise. We can also expect that domesticated lines of somatic cells will be important inputs to therapeutic applications of transplants.

Vaccination and Virogenic Therapy

Since 1798, vaccination has constituted an important medical application of the genetic modification of somatic cells by viruses, though its practitioners to this day are often oblivious to its mechanism. Jenner found that inoculation with infectious lymph caused a mild disease, cowpox, immunity to which also protected against the dangerous smallpox.

Many aspects of vaccination are still scientifically obscure, but we can now describe the process in terms of molecular genetics. The DNA of the cowpox virus is purposely introduced into certain cells which adopt the genetic information contained therein. These cells thereupon produce new gene products, encoded by the viral DNA, which stimulate other body cells to produce antibodies against them. The cross-immunity is then a byproduct of the virogenic alteration of some cells of the host.

Live viruses are now widely used for vaccination against many other diseases, including polio, measles, and—in special cases or in the near future—rubella, mumps, rabies, and so on.

Vaccination can be regarded as if it were a therapy to replace the functions of hypothetical genes not normally present in the human organism, those that would endogenously stimulate the formation of antibodies. This idea can be extended, in principle, to other gene products, for example, enzymes that may be missing in certain gene-defect diseases like phenylketonuria and perhaps diabetes. Laboratory models for this kind of virogenic therapy are being perfected and rational trials for human disease can be anticipated shortly (Rogers, 1970). Although basic genetic principles underlie this technique and the genetic apparatus of somatic cells is altered, it is classified as euphenic because the germ cells are left unchanged, and there should be no effects in future generations. This is a matter of empirical observation rather than necessary principle in biology, and it is quite conceivable that some inoculated virogenes might also be inherited, as has already been postulated for certain tumor viruses in rodents. This reservation applies with equal force to vaccination against infectious diseases about which we have little information in proportion to the enormous numbers of children involved.

The recent discovery of "reverse transcriptases," which copy RNA information back to DNA, promises to simplify some of the technical problems of developing virogenic agents. Differentiated cells should, under certain conditions, produce multiple copies of active messenger RNA molecules, and it will be easier to purify and test these than to attempt to dig out a single DNA gene from the complete chromosome set. (In due course, however, this should also be facilitated by knowing the chemical signals that distinguish the active from the inactive genes in a given cell.) Reverse transcription would then allow the recoding of the RNA message into DNA which would then be spliced to a virus for facilitated re-integration into chromosomes.

Virogeny will be in competition with cell transplants for the replacement therapy for genetic defects, but each may have special advantages in particular cases. For example, the transplantation of neurones is not likely to be very helpful except at the earlier stages of development.

Proposals for virogenic therapy reawaken many other questions about the use of live virus vaccines for mass prophylaxis — a public health measure that involves most of the world's population in contrast to the few subjects of experimental approaches to gene therapy. Inevitably, live viruses will carry a residual hazard of atypical reactions, and of passenger contaminants, al-

though these could be mitigated by more attentive research. On the other hand, the assumption that public smallpox vaccination can be safely abandoned is based on experience with the management of breakthroughs under almost optimum conditions. The notion that smallpox will be finally eradicated within the decade is hindered by serious geopolitical obstacles, and we do not know what would happen if the virus should be reintroduced (1) in unusually virulent form; (2) into populations who are immunologically relatively naive with respect to other infections as well as smallpox; and (3) under contingencies of breakdown of public health services. The 1972 epidemic may be a fortunate tocsin.

Viruses used for prophylaxis in man have been developed and monitored with scarcely more sophistication than that available to Jenner. The molecular biologist should insist that the highest standards of chemical and biological purity and characterization available in the research laboratory be applied to these agents. This will not be possible without a recognition that cheap vaccines will be worth what we pay. The drug companies cannot be faulted if higher standards are not imposed uniformly on their competitors.

Renucleation (Cloning)

From the work of Briggs and King (1952) and of Gurdon (1968), we know that an activated egg may be renucleated with a nucleus taken from a somatic cell of an existing frog. From a genetic standpoint, the new embryo is like a cutting, or clone, of a rose plant.

The question of renucleation of human eggs was first introduced (Lederberg, 1966) to make a rhetorical point. Many speculations had been put forward about the possibilities of "genetic surgery"—of a kind that would require fantastic innovations in our knowledge of molecular genetics. Renucleation in frogs had, however, been demonstrated long before, and it was also very plain that it would be available in man as a necessary prerequisite to more incisive techniques of genetic manipulation. It follows that, *if* one wishes to agonize about the likelier directions of futuristic change, he should attend to renucleation rather than genetic surgery.

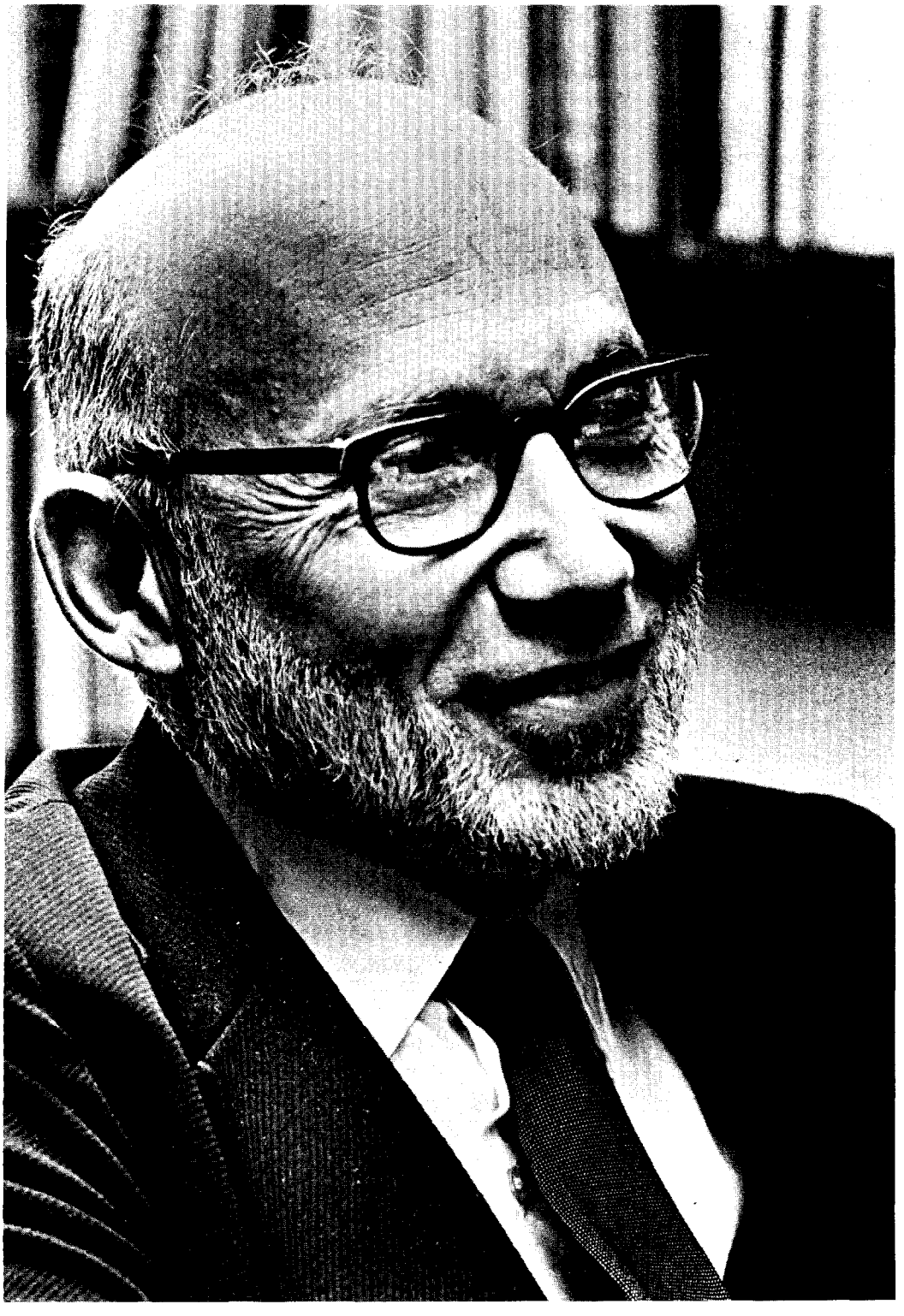
My erstwhile remarks that mice and men should not differ from frogs in amenability to renucleation may have been naive. Chromosome-inactivation, exemplified by the inactivation of one X in normal female cells, may play an even more important role in tissue differentiation in mammals compared to amphibia (Di Berardino and Hoffner, 1970). In that event, renucleation may not be technically possible until long after the achievement of other aspects of ontogenetic control which, in turn, may make renucleation relatively less useful for any practical problem.

We may still discuss "cloning" if only as a speculative exercise. If it could be done today, it is hard to see where renucleation would have very important applications, but this is precisely the kind of anticipatory study that needs to be done. On the positive side, it may give some otherwise sterile mates the opportunity of parenthood. An anovulatory woman might borrow an otherwise wasted egg cell, renucleate it with one of her own, or her husband's somatic cells, and have it reimplanted into her own uterus. Or a fertile wife might offer an intact egg for microsurgical fertilization with a haploid spermatocyte nucleus from her azoospermic husband.

We can properly understand the moral objections and justifications of such procedures only if we explore the whole continuum of technical interventions in human reproduction. Ever since primitive man discovered the connection between sexual intercourse and conception, human reproduction has entailed deliberate exercise of purpose and intelligence, an unavoidable power and responsibility for the next generation. The guarding of such responsibilities against external intrusions is the essence of personal freedom. It goes without saying that we would abhor state-enforced reproduction of any kind. Conversely, to what extent should individual patients be deprived of the possibility of using technical devices they, and their professional counselors, believe to be in their own and their offspring's interest?

Many unanswered questions remain on the ethical or technical merits of renucleation. Popular discussion of cloning has probably overemphasized the significance of a common genotype: Monozygotic twins are not copies of an identical personality, especially if they have been reared separately. They do resemble one another more closely than other relatives, to be sure, and renucleation could be a means of avoiding certain genetic defects that arise from segregation. If, for other valid reasons, renucleation is ever practiced, we can clear up many uncertainties about the interplay of heredity and environment; and students of human nature will not want to waste such opportunities. So many developmental hazards may be associated with renucleation that very extensive animal studies would be the minimum prerequisite to ethically justifiable trials in man, and the interval gives us ample time to ponder the values in balance.

Our consensual standards of an ethical medical experiment require that it serve a reasonable humanitarian purpose and that it have the informed consent of the individuals concerned. The problem of renucleation sets into relief the general problem of parenthood. Who else can speak for the welfare of the individual not yet in being? Should parents be held in contempt if they procreate despite the knowledge that they are risking a significant deformity in their offspring? Should they be encouraged to undertake artificial measures that will give their young an easier start? And where is the boundary line between the responsibility



DR. JOSHUA LEDERBERG, *a native of Montclair, New Jersey, and a product of New York City public schools, Columbia University, and Yale, won a 1958 Nobel Prize "for studies on organization of the genetic material in bacteria." Dr. Lederberg is Joseph D. Grant professor of genetics and biology and chairman of the Department of Genetics of the Stanford University School of Medicine. He is also director of the Lt. Joseph P. Kennedy, Jr. Laboratories for Molecular Medicine, dedicated to basic research in genetics, developmental biology, and neurobiology for a broad attack on the problem of mental retardation. He has related responsibilities for research programs in instrumentation, computers for laboratory use and in the study of mechanized intelligence, and the detection of planetary life. Both he and Dr. Elliott Levinthal, director of the Instrumentation Research Laboratory in the genetics department, are participating in the design of science packages to carry out exploration of Mars on Viking '75 Project missions planned by the National Aeronautics and Space Administration.*

of the parent and of the community for manipulating a child's development—the socialization or education that predestines him to function as a particular kind of human being?

These questions are properly applied to the destinies of particular individuals born day by day. Gloomy predictions about the long-range future of the species might be substantiated as a side effect of medical care and other welfare measures that avert the pain of natural selection. However, the pace of discovery in genetics is so rapid, compared to that of biological evolution, that we can afford to wait another 50 or 100

years before we tackle the species problem. We will then have sharper tools and, at least, as much wisdom about how to use them. Meanwhile, we have enough to do in trying to minimize the enormous burden of personal distress and anxiety that attends our genetic load as it is manifest birth by birth, death by death. Indeed, it is hard to see how we can make better substantial progress toward an ideal of human improvement than by freeing individual families of the anxiety and the burden of known defects. The general questions of human improvement (Lederberg, 1971*a*) apply with equal force to policies of education and even to the standards of health and nutrition promulgated by pediatricians.

Summary

Advances in molecular biology promise to enlarge our technical capacity to intervene in genetic problems. Social and ethical factors are, therefore, likely to play an increasingly important role in determining the application of new scientific advances in man. This is no cause for great alarm, for the same principle already applies to the use of surgery and of other medical interventions that could, in theory, also be applied for extraordinary "renovations" of human nature.

The evolution of wise policies for the use of genetic advances, and the surveillance of existing practices for compliance with consensual ethical standards, and for the anticipation of social injury, of course, require a widely disseminated understanding of the probable potentialities of various types of genetic intervention.

The most important influences on the genetic composition of the human species are likely to remain side effects of other global policies: the movement of populations, transportation technology, the effects of war and of discrepancies in economic development and attention to preventive genetic hygiene, especially through the identification and elimination of principal environmental sources of gene mutation.

Specific options for genetic therapy include the rapidly developing field of antenatal diagnosis (coupled with elective abortion of threatened fetuses); cell and organ transplantation; and virogenic therapy. The last would entail the introduction of desired DNA segments into domesticated strains of viruses; these would then serve for the vaccination of patients lacking a critical metabolic function which would then be restored under the influence of the added DNA.

The renucleation of eggs (cloning) is also a theoretical possibility, likely to be of more metaphorical than pragmatic interest. The discussion of cloning may help to illuminate the ethical problem of parenthood, generally: What is the responsibility of each generation for the biological and educational predetermination of its successors?

In any event, the central responsibility of the geneticist, *qua* physician, is to the welfare of his individual patients.

References

I could not pretend to have mastered all of the works that would have to be cited in a comprehensive bibliography of the subjects of this paper. Indeed, the central issues might be obscured more than clarified by too detailed an elaboration.

A comprehensive bibliography on *bioethics* is maintained by the Kennedy Center for Bioethics, Georgetown University, Washington, D.C.

Further references may be found in the bibliographies of the papers cited here and by using these, in turn, as keys for a citation-index search of current literature. This list of references has been limited to secondary sources and to a few titles essential for the clarity of the text. The most secure prediction that can be made about the near future is the early obsolescence of this bibliography.

Aron, R. 1968. *Progress and Disillusion—the Dialectics of Modern Society*. Signet (N.A.L.), New York.

Auerbach, C. and J. M. Robson. 1944. Production of mutations by allyl isothiocyanate. *Nature*, 154: 81–82.

Briggs, R. and T. J. King. 1952. Transplantation of living nuclei from blastula cells into enucleated frogs eggs. *Proceedings of the National Academy of Sciences, Washington*, 38: 455–63.

Davis, B. D. 1970. Prospects for genetic intervention in man. *Science*, 170: 1279–83.

Di Berardino, M. A. and N. Hoffner. 1970. Origin of chromosomal abnormalities in nuclear transplants—a re-evaluation of nuclear differentiation and nuclear equivalence in amphibians. *Developmental Biology*, 23: 185–209.

Dorfman, A. (ed.). 1972. *Antenatal Diagnosis*. University of Chicago Press, Chicago.

Feigenbaum, E. A., B. G. Buchanan, and J. Lederberg. 1971. On generality and problem solving: A case study using the DENDRAL program. *Machine Intelligence*, 6: 165–90.

Gurdon, J. B. 1968. Transplanted nuclei and cell differentiation. *Science*, 219: 24–36.

Harris, H. 1970. *Cell Fusion*. Harvard University Press, Cambridge, Mass.

IAEA Panel. 1969. New approaches to breeding for improved plant protein. International Atomic Energy Agency, Vienna.

Lederberg, J. 1966. Experimental genetics and human evolution. *American Nature*, 100: 519–31.

———. 1971*a*. Orthobiosis: the perfection of man. In: A. Tiselius and S. Nilsson (eds.). *The Place of Value in a World of Facts*. Nobel Symposium XIV. Wiley Interscience, New York, pp. 29–58.

———. 1971*b*. Biomedical frontiers: genetics. In: *The Challenge of Life*. Roche Jubilee Symposium, Basel, Switzerland.

———. 1972. The freedoms and the control of science: notes from the ivory tower. *Southern California Law Review*, 45: 569–614.

Ramsey, P. 1970. *Fabricated Man — the Ethics of Genetic Control*. Yale University Press, New Haven, Conn.

Rogers, S. 1970. Skills for genetic engineers. *New Scientist*, 45: 194–96.

——— and P. Pfuderer. 1968. Use of viruses as carriers of added genetic information. *Nature*, 219: 749.